Peer Review
Experimental Toxicology Division
N H E E R L

WATER

Factors that Influence the in vivo Disposition of Arsenic in the Mouse

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Introduction

Inorganic arsenic (iAs) is a natural drinking water contaminant. Human exposure to drinking water contaminated with iAs is associated with the development of cancer in skin and internal organs. The absorption and metabolism of iAs may result in the exposure to six different arsenicals, each having a unique toxicological profile. There are many factors such as dose and nutritional status that may affect the metabolism of iAs and the subsequent formation of the other arsenicals.

Aims

The aims of our studies are to examine factors that may affect the metabolism and disposition of iAs and its methylated metabolites. Factors studied included dose, dietary selenium, polymorphisms in methylation, and acute vs. repeated exposure.

Methods

Model: Adult female mouse

Chemicals: arsenate, arsenite, monomethylarsonic acid (MMA(V)) or dimethylarsinic acid (DMA(V)); ^{14}C, ^{73}As, or unlabeled

Route: oral, intravenous

Dose: 0.4 to 60 mg As/kg

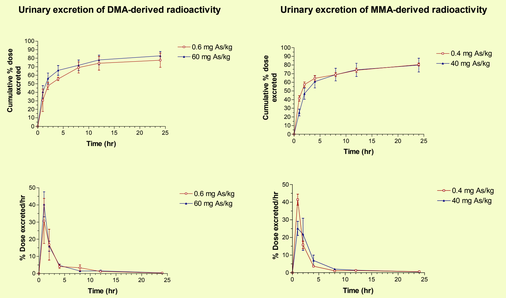
Exposure: acute; repeated daily oral exposure

Endpoint: Collection and analysis of excreta and tissues for arsenic by liquid chromatography, liquid and gamma scintillation spectroscopy, and hydride generation atomic absorption spectrometry; thioredoxin activity

Other: In one experiment, mice were placed on diets to alter their selenium status.

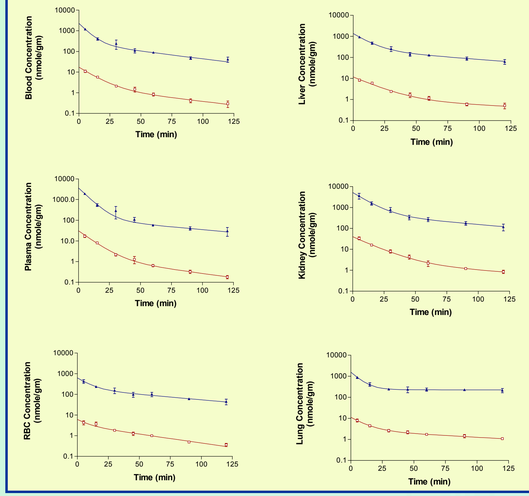
Effect of administered dose on iv disposition of DMA and MMA

Both chemicals are rapidly excreted in urine; other than methylation of MMA to DMA, dose did not affect the disposition of these arsenicals.



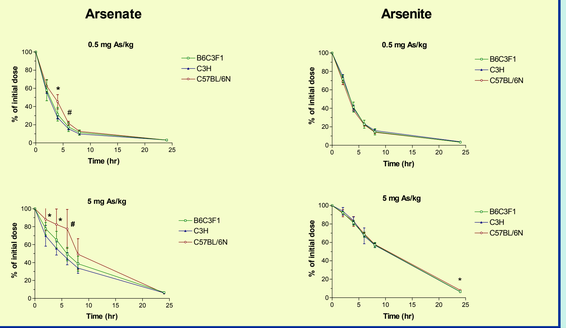
Effect of iv dose on tissue disposition of DMA

A rapid biexponential decrease in tissue DMA was observed; DMA was not metabolized; retention of DMA in lung was dose-dependent.



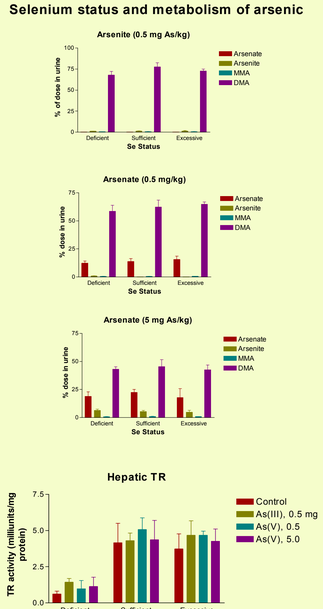
Effect of strain and dose on oral disposition of arsenate and arsenite

Whole-body retention of arsenate at early times affected by strain; dose-dependent effect on whole-body retention of inorganic arsenic



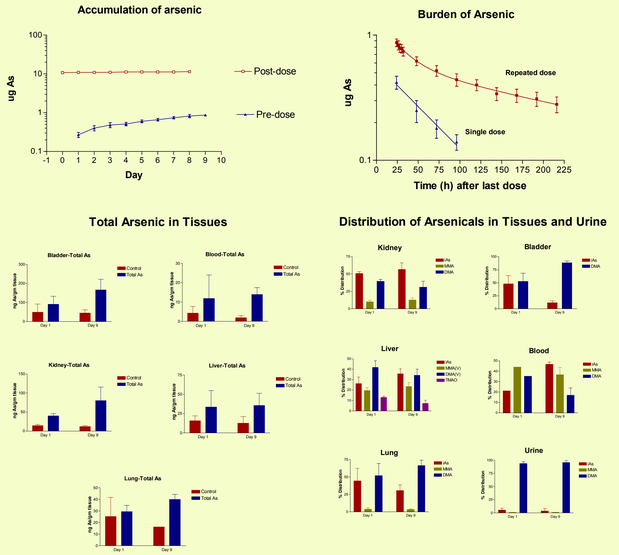
Effect of selenium status on disposition of arsenate and arsenite and thioredoxin activity

There was a trend toward lower cumulative DMA urinary excretion in Se-deficient mice at the low iAs dose; hepatic thioredoxin reductase activity was significantly increased in Se-deficient mice treated with arsenite compared to untreated Se-deficient mice



Effect of repeated oral exposure of arsenate

Arsenic accumulated in tissues of mice after repeated exposure to arsenate. A tissue specific accumulation of total and speciated arsenic occurs after this repeated exposure. The arsenicals excreted in urine do not reflect the dosimetry of tissue arsenicals.



Conclusions

Dose, dietary selenium and repeated exposure to arsenate are factors that influence the disposition of arsenic in the mouse

Impact: This information describing arsenic exposure and tissue dose in rodents and factors that affect it can assist in making predictions of arsenic exposure and tissue dose in humans.

Future Directions: We plan to examine the oral disposition of MMA and DMA for PBPK model development and validation. We also plan to examine the effect of age on the disposition of arsenic.

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